AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph at page 4, lines 23-28, with the following paragraph:

Figure 4 shows an image of an array signal from yeast genomic DNA assayed on a BEADARRAY™ [BeadArray™] (Panel A) and a subset of perfect match (PM) and mismatch (MM) intensities for 18 loci out of 192 assayed from four different quadruplicate arrays (R5C1,R5C2,R6C1,R6C2) (Panel B). The PM probes are the first set of four intensity values and MM probes are the second set of four intensity values denoted by each probe type label on the lower axis.

Please replace the paragraph at page 4, lines 29-30, with the following paragraph:

Figure 5 shows array-based SBE genotyping performed on human gDNA directly hybridized to BEADARRAYS™ [BeadArrays™].

Please replace the paragraph at page 5, lines 1-4, with the following paragraph:

Figure 6 shows array-based ASPE genotyping performed on human gDNA directly hybridized to a BEADARRAY™ [BeadArray™]. Panel A shows raw intensity values across the 77 probe pairs and Panel B shows the discrimination ratios (PM/PM+MM) plotted for the 77 loci.

Please replace the paragraph at page 5, lines 5-9, with the following paragraph:

Figure 7 shows Genotyping scores of unamplified genomic DNA compared to random primer amplified (RPA) genomic DNA using the GOLDENGATE® [GoldenGate™] assay (the amount of DNA input in the RPA reaction is shown below each bar, the RPA reactions employed random 9-mer oligonucleotides, except where the use of hexanucleotides (6-mer) or dodecanucleotides (12-mer) are specified).

Please replace the paragraph at page 5, lines 15-18, with the following paragraph:

Figure 11 shows, in Panel A, an image of a BEADARRAY™ [BeadArray™] hybridized with genomic DNA fragments and detected with ASPE, and in Panel B, a GenTrain plot in which two homozygous (B/B and A/A) clusters and one heterozygous (A/B) cluster at one locus are differentiated.

Please replace the paragraph at page 6, line 29, through page 7, line 6, with the following paragraph:

Figure 14 shows scatter plots for Klenow-primed ASPE reactions on BEADARRAYS™ [BeadArrays™] comparing assay signal in the presence and absence of single stranded binding protein (SSB). The scatter plot in panel A shows the effect of SSB on ectopic signal intensity in the absence of amplified genomic DNA, whereas the scatter plot in panel B shows the effect of SSB on signal intensity in the presence of amplified genomic DNA. Panels C and D show plots of the intensity for loci (sorted in order of increasing intensity) for either Klenow (Panel C) or Klentaq (Panel D) ASPE reactions run on BEADARRAYS™ [BeadArrays™] in the absence of an amplified population of genome fragments (ntc – no target control provides a measure of "ectopic" extension).

Please replace the paragraph at page 59, line 28, through page 60, line 12, with the following paragraph:

In a particular embodiment, arrayed nucleic acid probes can be modified while hybridized to genome fragments for detection. Such embodiments, include, for example, those utilizing ASPE, SBE, oligonucleotide ligation amplification (OLA), extension ligation (GOLDENGATE® [GoldenGate™]), invader technology, probe cleavage or pyrosequencing as described in US Pat. No. 6,355,431 B1, US Ser. No. 10/177,727 and/or below. Thus, the invention can be carried out in a mode wherein an immobilized probe is modified instead of a genome fragment captured by a probe. Alternatively, detection can include modification of the genome fragments while hybridized to probes. Exemplary modifications include those that are catalyzed by an enzyme such as a polymerase. A useful modification can be incorporation of one or more nucleotides or nucleotide analogs to a primer hybridized to a template strand,

wherein the primer can be either the probe or genome fragment in a probe-genome-fragment hybrid. Such a modification can include replication of all or part of a primed template. Modification leading to replication of only a part of a template probe or genome fragment will be understood to be detection without amplification of the template since the template is not replicated along its full length.

Please replace the paragraph at page 66, lines 4-12, with the following paragraph:

Alternatively, an extension ligation (GOLDENGATE® [GoldenGate™]) assay can be used wherein hybridized probes are non-contiguous and one or more nucleotides are added along with one or more agents that join the probes via the added nucleotides. Exemplary agents include, for example, polymerases and ligases. If desired, hybrids between modified probes and targets can be denatured, and the process repeated for amplification leading to generation of a pool of ligated probes. As above, these extension-ligation probes can be but need not be attached to a surface such as an array or a particle. Further conditions for extension ligation assay that are useful in the invention are described, for example, in US Pat. No. 6,355,431 B1 and US App. Ser. No. 10/177,727.

Please replace the paragraph at page 90, line 20, through page 91, line 4, with the following paragraph:

Several of the methods exemplified herein with respect to detection of typable loci of genomic DNA can also be applied to gene expression analysis. In particular, methods for on-array labeling of probe nucleic acids using primer extension methods can be used in the detection of RNA or cDNA. Probe-cDNA hybrids can be detected by polymerase-based primer extension methods as described herein previously. Alternatively, for array-hybridized mRNA, reverse-transcriptase-based primer extension can be employed. There are several non-limiting advantages of on-array labeling for gene expression analysis. Labeling costs can be dramatically decreased since the amounts of labeled nucleotides employed are substantially less compared to methods for labeling captured targets. Secondly, cross-hybridization can be dramatically reduced since a target must both hybridize and also contain perfect complementarity at its 3'

terminus for label incorporation in a primer extension reaction. Similarly, OLA or GOLDENGATE® [GoldenGate™] assays can be used for detection of hybridized cDNA or mRNA. The latter two methods typically require addition of an exogenous nucleic acid for each locus queried. However, such methods can be advantageous in applications where the use of primer extension leads to unacceptable levels of ectopic extension.

Please replace the title at page 97, lines 5-7, with the following title:

EXAMPLE II

Detection of Yeast Loci for a Yeast Whole Genome Sample Hybridized to BEADARRAYS™ [BeadArrays™]

Please replace the paragraph at page 97, lines 8-10, with the following paragraph:

This example demonstrates reproducible detection of yeast loci for a yeast whole genome sample hybridized to a BEADARRAYS™ [BeadArrays™] and probed with allele-specific primer extension (ASPE).

Please replace the paragraph at page 97, lines 11-23, with the following paragraph:

Six hundred nanograms of random primer amplified (RPA) yeast gDNA was hybridized to a locus-specific BEADARRAY™ [BeadArray™] (Illumina). The BEADARRAY™ [BeadArray™] was composed of 96 oligonucleotide probe pairs (PM and MM, 50 bases in length) interrogating different gene-based loci distributed throughout the S. cerevisiae genome. The amplified yeast genomic DNA was hybridized to the BEADARRAY™ [BeadArray™] under the following conditions: Overnight hybridization at 48 °C in standard 1X hybridization buffer (1 M NaCl, 100 mM potassium-phosphate buffer (pH 7.5), 0.1% Tween 20, 20% formamide). After hybridization, arrays were washed in 1X hybridization buffer at 48 oC for 5 min. followed by a wash in 0.1 X hybridization buffer at room temperature for 5 min. Finally, the array was washed for 5 min. with ASPE reaction buffer to block and equilibrate the array before the extension step. ASPE reaction buffer (10 X GG Extension buffer (Illumina, Inc., San

Diego, CA), 0.1% Tween-20, 100 ug/ml BSA, and 1 mM dithiothreitol, 10% sucrose, 500 mM betaine).

Please replace the paragraph at page 97, line 24, through page 98, line 11 with the following paragraph:

An ASPE reaction was performed directly on the array as follows. The BEADARRAY™ [BeadArrays] were dipped into 50 uls of an ASPE reaction mix containing the described ASPE reaction buffer supplemented with 3 uM dNTPs (1.5 uM dCTP), 1.5 uM biotin-11-dCTP, ~0.4 ul Klentaq (DNA Polymerase Technology, Inc, St. Louis, MO, 63104). The BEADARRAYS™ [BeadArrays™] were incubated in the ASPE reaction for 15 min. at room temperature. The BEADARRAYS™ [BeadArrays™] were washed in fresh 0.2 N NaOH for 2 min., then twice in 1X hybridization buffer for 30 sec. The incorporated biotin label was detected by a sandwich assay employing streptavidin-phycoerythrin and biotinylated anti-streptavidin staining. This was done as follows: BEADARRAYS™ [BeadArrays™] were blocked at room temperature for 30 min in casein block (Pierce, Rockford, IL). This was followed by a quick wash (1 min.) in 1X hybridization buffer, before staining for 5 min. at room temp. with streptavidin-phycoerythrin (SAPE) solution (1X hybridization buffer, 0.1% Tween 20, 1 mg/ml BSA, 3 ug/ml streptavidin-phycoerythrin(Molecular Probes, Eugene, OR). After staining, the BEADARRAYS™ [BeadArrays™] were quick washed with 1X Hyb. buffer before counterstaining with 10 ug/ml biotinylated anti-streptavidin antibody (Vector Labs, Burlingame, CA) in 1X TBS supplemented with 6 mg/ml goat serum, Casein and 0.1% Tween 20. This step was followed by a quick wash in 1X Hyb. buffer, and than a second staining with SAPE solution as described. After staining, a final wash in 1X Hyb. buffer was performed.

Please replace the title at page 99, lines 1-3, with the following title:

EXAMPLE III

Whole Genome Genotyping (WGG) of Human gDNA Directly Hybridized to BEADARRAYS™ [BeadArrays™].

Please replace the paragraph at page 99, lines 9-18, with the following paragraph:

Human placental genomic DNA samples were obtained from Coriell Inst. Camden, NJ. The human placental gDNA sample (150 ug) was hybridized to a BEADARRAY™ [BeadArray™] (Illumina) having 4 separate bundles each containing the same set of 24 different non-polymorphic probes (50-mers). The BEADARRAY™ [BeadArray™] consisted of 96 probes to human non-polymorphic loci randomly distributed throughout the human genome. The probes were 50 bases long with ~ 50% GC content and designed to resequence adjacent A (16 probes), C (16 probes), G (16 probes), or T (16 probes) bases. DNA samples (150 ug human placental DNA) were hybridized overnight at 48 °C in standard 1X hybridization buffer (1 M NaCl, 100 mM potassium-phosphate buffer (pH 7.5), 0.1% Tween 20, 20% formamide) in a volume of 15 ul.

Please replace the paragraph at page 99, lines 19-29, with the following paragraph:

Four separate SBE reactions were performed directly on the array, one for each separate bundle, as follows. The "A" reaction contained biotin-labeled ddATP and unlabeled ddCTP, ddGTP, and ddTTP. The other three SBE reactions were similar except that the labeled and unlabeled designations were adjusted appropriately. The SBE reaction conditions were as follows: The BEADARRAYS™ [BeadArrays™] were dipped into an SBE reaction mix at 50oC for 1 min. Four different SBE reaction mixes were provided, an A, C, G, or T resequencing mix. For example, a 50 ul A-SBE resequencing mix contained 1 uM biotion-11-ddATP (Perkin Elmer), 1 uM ddCTP, 1 uM ddGTP, and 1 uM ddUTP, 1X Thermosequenase buffer, 0.3 U Thermosequenase, 10 ug/ml BSA, 1 mM DTT, and 0.1% Tween 20. The other three SBE mixes were similar with the appropriate labeled base included and the other bases unlabeled.

Please replace the paragraph at page 100, lines 6-14, with the following paragraph:

A similarly prepared human placental gDNA sample (150 ug) was hybridized to a BEADARRAY™ [BeadArray™] containing 77 functional perfect match (PM) and mismatch (MM) probe pairs querying non-polymorphic loci. The ASPE probes were designed to non-

polymorphic sites within the human genome. The probes were 50 bases in length with ~ 50% GC content. The perfect match (PM) probes were completely matched to genomic sequence whereas the mismatch (MM) probes contained a single base mismatch to the genomic sequence at the 3' base. The mismatch type was biased towards modeling A/G and C/T polymorphisms. The hybridization and reaction conditions were as previously described in Example II.

Please replace the paragraph at page 100, lines 15-29, with the following paragraph:

An allele-specific primer extension reaction (ASPE) was performed directly on the array surface, and the incorporated biotin label detected with streptavidin-phycoerythrin staining. The ASPE reaction was performed as follows. BEADARRAYS™ [BeadArrays™] were washed twice in 1X hybridization buffer and then washed with ASPE reaction buffer (without enzyme and nucleotides) at room temperature. The ASPE reaction was carried out by dipping the BEADARRAYS™ [BeadArrays™] into a 50 ul ASPE reaction mix at room temperature for 15 minutes. The ASPE mix contained the following components: 3uM dATP, 1.5 uM dCTP, 1.5 uM biotin-11-dCTP, 3 uM dGTP, 3 uM dUTP, 1x GOLDENGATE® [GoldenGate™] extension buffer (Illumina), 10% sucrose, 500 mM betaine, 1 mM DTT, 100 ug/ml BSA, 0.1% Tween 20 and 0.4 ul Klentaq (DNA Polymerase Inc., St. Louis, MO). Figure 6A shows the raw intensity values across the 77 probe pairs. The PM probes (squares) exhibit much higher intensities than the MM probes across a majority of the probes effectively allowing the queried base to be distinguished. Figure 6B shows a plot of the discrimination ratios (PM/PM+MM) for the 77 loci. These results demonstrated that about two thirds of the loci had ratios > 0.8.

Please replace the paragraph at page 101, lines 14-19, with the following paragraph:

The amplified population of genome fragments was genotyped as follows. The genotyping was performed by Illumina's SNP genotyping services using the proprietary GOLDENGATE® [GoldenGate™] assay on Illumicode [IllumiCodeTM] arrays. The GenTrain score is a metric for how well the genotype intensities of the SNP loci cluster across a sample population. A comparison of GenTrain score to the unamplified control provides an estimate of locus amplification and bias.

Please replace the paragraph at page 102, lines 10-16, with the following paragraph:

A set of 3 X 32 DNA samples (1 ug each) were amplified by random primer amplification to produce separate target samples having 150 ug of genomic DNA fragments. The amplified populations of fragments were hybridized to BEADARRAYS™ [BeadArrays™] having 50-mer ASPE capture probes covering 192 loci. After hybridization, an ASPE reaction was performed as described in Example III. Images were collected and genotype clusters analyzed using proprietary GenTrain software (Illumina). An exemplary image of a BEADARRAY™ [BeadArray™] detected with ASPE is shown in Figure 11A.

Please replace the paragraph at page 103, lines 3-6, with the following paragraph:

Exemplary GenTrain plots for two different loci are shown in Figures 12C and 12D. This data shows that for the majority of samples, three clusters were clearly differentiated corresponding to homozygous (B/B and A/A) and (A/B) genotypes. The two grey points are from "no target control" BEADARRAYS™ [BeadArrays™].

Please replace the paragraph at page 103, line 25, through page 104, line 3, with the following paragraph:

Figure 14A shows a scatter plot for an ASPE reactions run with Klenow polymerase on BEADARRAYS™ [BeadArrays™] in the presence of SSB and absence of a target nucleic acid sample (ntc=no target control). As demonstrated by Figure 14C, ectopic signal was greatly reduced in the presence of SSB compared to in the absence of SSB. Similar results were obtained for ASPE reactions run with Klentaq polymerase. The plots shown in Figures 14C and D were obtained by sorting signals from scatter plots along the X-axis according to increasing intensity. As shown in Figure 14B, allele specific extension occurred at detectable levels for ASPE reactions carried out in the presence of a target sample containing an amplified population of genome fragments.